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DOI: https://doi.org/10.2478/9788376560564.c4

Chapter 4

Histamine Receptors and Inflammatory Cells

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4.1. Introduction

Up to now, four subtypes of human histamine receptors (HR)s have been identified: H_1R, H_2R, H_3R, and H_4R, all of them being GPCRs with seven transmembrane (TM)-spanning helices, which are expressed on various cell types.

The H_1R is expressed upon various cell types including eosinophils (Simons & Akdis, 2009). This receptor plays a significant role in allergic inflammation and immune modulation, as it increases the release of histamine and other

mediators, chemotaxis of eosinophils and neutrophils, and enhances the antigen-presenting capacity and co-stimulatory activity of B cells.

H_2R has a key role in stimulating gastric acid secretion (Code, 2008; Hill *et al.,* 1997) while also posessing immunoregulatory effects (Akdis & Simons, 2006) and a role in allergic inflammatory responses by mediating mucus production in the airway, vasodilation, and bronchial smooth muscle relaxation (Parsons & Ganellin, 2006). Histamine via H_2R differentially reduces fMLP[1]-induced O_2^- generation in neutrophils and eosinophils (Reher *et al.,* 2012). Selective H_2R antagonists (famotidin, tiotidine and zolantadine) reduce histamine-induced effects of induction of intracellular cAMP accumulation in neutrophils and eosinophils (Reher *et al.,* 2012).

Classically H_3R acts as a presynaptic auto-receptor that inhibits the synthesis and release of histamine in the histaminergic neurons in the central nervous system (CNS) (Martinez-Mir *et al.,* 1990). H_3R is also highly expressed in eosinophils, dendritic cells and monocytes (Simons & Akdis, 2009), while low amounts are expressed in the peripheral tissues (Hill *et al.,* 1997). Activation of H_3R inhibits adenylate cyclase, reduces production of cAMP and inhibits Ca^{2+} influx (Gaudy-Marqueste, 2010). Histamine through H_3R may increase pruritus without the involvement of mast cells and also increase nasal congestion (Simons & Akdis, 2009). Selective agonists are in development for the disorders of central nervous system (Simons & Akdis, 2009). Chemotaxis of eosinophils via H_3R was controversial (Raible *et al.,* 1994); however, recent studies (see below) suggest that the newly described receptor, H_4R, mediates this effect.

The H_4R is a relatively novel histamine receptor structurally and pharmacologically related to the H_3R receptor (Liu *et al.,* 2001). H_4R is highly expressed in various cells of the immune system such as bone marrow and peripheral hematopoietic cells, eosinophils, mast cells, neutrophils, dendritic cells, T-cells and basophils (Parsons & Ganellin, 2006). H_4R mediates the chemotaxis of mast cells and eosinophils *in vivo*. Histamine through H_4R can increase calcium flux in human eosinophils (Simons & Akdis, 2009), and together with H_2R it can increase the IL-16 release from the lymphocyte (Parsons & Ganellin, 2006).

This chapter address the role of histamine and in particular that mediated by the H_4R receptor in different immune cells involved in the innate response. The role and function of the cells are described followed by an examination of the effects of histamine on the cells.

1 N-formyl-methionyl-leucyl-phenylalanine

4.2. Mast cells and Basophils

Mast cells and basophils are considered to be major allergic effector cells and are generated from CD34+ stem cells, which are produced in the bone marrow (reviewed in Schroeder, 2011; Metcalfe, 2008; Falcone *et al.,* 2011). Although both cell types share many morphological features and functions, basophils mature and are released into the blood from the bone marrow while mast cells arise from precursors that usually mature within tissues such as the skin, lung and gastrointestinal tract. Mast cells depend on stem cell factor (SCF), a cytokine produced by eosinophils, bone marrow endothelial cells and fibroblasts, for their survival, proliferation and maturation *in vitro* (Piliponsky *et al.*, 2002). Mast cells are relatively large and their cytoplasm is highly granulated (Figure 4.1). These granules contain and release pharmacologically active compounds such as histamine, tryptase, chymase and proteoglycans (Galli *et al.,* 2008). In humans, granules of tissue mast cells may contain either tryptase alone (found in lung alveoli, small intestinal mucosa and the mucosa in allergic eye disease) or tryptase together with mast cell-specific chymase, cathepsin G and carboxypeptidase A (mainly located in normal skin, blood vessels, the submucosa, and synovium) (Hsu & Boyce, 2009). A specific growth factor for basophils has not yet been discovered but they can be grown *in vitro* from CD34+ cells using IL-3, although in mice this cytokine exhibits some degree of redundancy since IL-3 knockout mice still produce some basophils (Lantz *et al.*, 1998; Shen *et al.*, 2008).

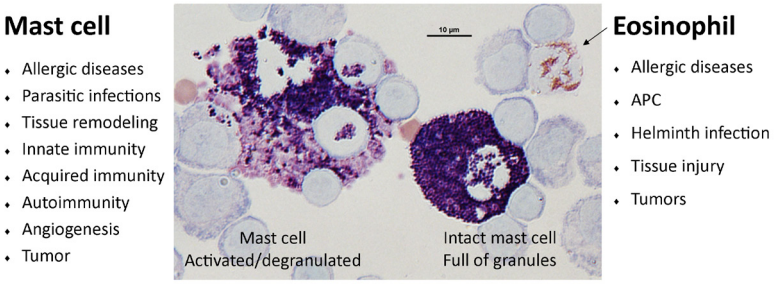

Figure 4.1 Mast cells and eosinophil from the peritoneal lavage of CD48 knockout mice stained with Giemsa. Mast cells, full of granules are stained in violet color and one eosinophil on the top right corner is stained orange-purple. The key functions of the mast cells are written on the left and those of eosinophil on the right.

4.2.1. Function

Basophils migrate from the blood into tissues affected by allergic inflammation (reviewed in Falcone, Knol & Gibbs, 2011). These cells, along with their tissue-fixed mast cell counterparts are major sources of histamine in humans, which

is rapidly released upon allergen binding to antigen-specific IgE when bound to high affinity IgE receptors (FcεRI). Allergen-mediated activation of mast cells and basophils also results in the release of a large number of inflammatory mediators that govern the signs and symptoms of allergy. These include the release of eicosanoids (primarily PGD2 and LTC4, where mast cells release both and basophils release only LTC4) and various inflammatory cytokines. In humans, basophils are particularly prominent sources of the Th2-type cytokines IL-4 and IL-13, which cause IgE class switching in B cells leading to polyclonal IgE synthesis (Yanagihara *et al.,* 1998) whereas mast cells generate IL-8 and TNF-α (Gibbs *et al.,* 2001). These cell types, therefore, not only contribute to the symptoms of acute allergic inflammation but also appear to play immunomodulatory roles in supporting pro-allergic immunity (particularly basophils) and inflammation associated with allergic disease. These cells also respond to infections with certain parasites and it is thought that their main biological function may be related to parasite expulsion (Falcone *et al.,* 2001; Knight *et al.,* 2008), although their exact biological roles are still poorly understood.

Mast cells together with dendritic cells are the first immune system cells that respond to and interact with antigens, invading pathogens or environmentally derived toxins. Mast cells can enhance host resistance by promoting clearance of bacteria during several bacterial infections (Kalesnikoff & Galli, 2008; Piliponsky *et al.,* 2010; Thakurdas *et al.,* 2007). FcεRI mediates important interactions between mast cells and bacteria. IgE antibodies against *Staphylococcus aureus* or its toxin have been found in patients suffering from atopic dermatitis (Bunikowski *et al.,* 1999; Friedman *et al.,* 1985; Motala, *et al.,* 1986). These reports suggest that mast cells have an important role in bacterial infection. Mast cells are also thought to have some role in autoimmunity (Eller & Rosenkranz, 2012). New models are being developed for studying mast cell functions *in vivo* (Reber *et al.,* 2012) to help understand their role in pathophysiology.

4.2.2. Histamine and Other Biogenic Amines in Mast Cell Pathophysiology

Mast cells are the major histamine producers in humans (Schneider *et al.,* 2010). As in other important histamine producing cells, such as histaminergic neurons and enterochromaffin-like cells (ECLC), the newly synthesized histamine is stored in specialized vesicles until a stimulus promotes exocytosis (Woska & Gillespie, 2012). The enzyme responsible for histamine synthesis, histidine decarboxylase (HDC, EC 4.4.4.22), is associated with the internal membrane of endoplasmic reticulum (ER) in its active form (Suzuki *et al.,* 1998; Moya-García *et al.,* 2005; Furuta *et al.,* 2006). Thus, the first location of nascent histamine must be the ER lumen. From there, histamine is conducted to specialized granules. This raises the question of why histamine needs to be partitioned from the

other intracellular components. Histamine is a mono- or dication depending on the polarity of the environment, due to the presence of an imidazole moiety. Imidazole groups are often involved in acid/base catalytic reactions as well as in electrostatic binding to aromatic moieties of many different macromolecules with specific functional consequences (Pilbak, *et al.,* 2012; Mutti *et al.,* 2011). These chemical characteristics may explain why a cell producing large amounts of histamine has evolved to keep this reactive amine separate from other molecules in the cytoplasm. In addition to 5 membrane receptors (histamine receptors 1-4 and N-methyl aspartate receptor), histamine can bind to several types of ion transporters, members of Cytochrome P450 (Cyp) family, and nucleic acids (Ruiz-Chica *et al.*, 2006; Schneider *et al.,* 2010).

An increase in free, newly synthesized histamine leads to a decrease in the cellular growth rate, as demonstrated in transfected cell cultures unable to store the amine in appropriate vesicles (Abrighach *et al.*, 2010), where the G1/S transition is blocked in HEK cells transfected to express active HDC. This could explain the lack of stable transfected cell models overexpressing active mammalian HDC. These observations on transfected cultured cells are consistent with the fact that histamine is not actively produced by mast cell precursors during the first stages of mouse bone marrow cell differentiation *in vitro*, when more active cell proliferation occurs (García-Faroldi *et al.,* 2009a). This suggests an antiproliferative role for newly synthesized free histamine in mammalian cells.

Mast cell granules are mainly composed of several mast cell specific proteases (e.g. tryptase and chymase), peptidoglycans (e.g. serglycin), and biogenic amines. However, histamine is not the only biogenic amine present in mast cell granules. Some rodent mast cell subsets contain serotonin (the decarboxylation product of the HDC paralogue, the aromatic L-amino acid decarboxylase or dopa decarboxylase (DDC, EC 4.1.1.28) (Moya-García *et al.,* 2005). In addition, polyamines are essential for normal mast cell differentiation (García-Faroldi *et al.*, 2010). The natural polyamines, putrescine, spermidine and spermine are ubiquitous aliphatic amines that have low molecular weight and are highly charged cations under physiological conditions. Putrescine is formed by decarboxylation of ornithine, a reaction catalysed by the enzyme ornithine decarboxylase (ODC, EC 4.1.1.17). Higher polyamines, spermidine and spermine, are synthesized by adding an aminopropyl group from decarboxylated S-adenosyl-methionine to putrescine and spermidine, respectively (Urdiales *et al.*, 2001). Spermidine and spermine are polycations (3 and 4 positive charges at physiological pH) able to interact with anionic macromolecules, such as nucleic acids and proteoglycans (Belting *et al.,* 2003; Poulin *et al.,* 2012; Ruiz-Chica *et al.,* 2001a-b and 2003), and other protein targets for histamine (e.g. NMDA receptor and CytP450) (Colwell & Levine, 1997; LaBella & Brandes, 2000). Taking into account these chemical and docking properties, it is not surprising

that polyamines contribute to the normal mast cell granule conformation as is the case for the other biogenic amines, histamine and serotonin (Ringvall *et al.*, 2008; Rönnberg *et al.,* 2012). Thus, mast cells provide an excellent model to study the biochemical and physiological interplay among biogenic amines (Medina *et al.*, 2005; Sánchez-Jiménez *et al.*, 2007).

Higher polyamines are essential to maintain cell proliferation and viability (Kahana, 2009; Pegg, 2009). In contrast, excess of non-compartmentalized histamine can be an anti-proliferative factor (Abrighach *et al.*, 2010). In addition, an excess of free polyamines can be deleterious as a source of reactive oxygen species and toxic aldehydes produced during their degradation (Babbar *et al.*, 2007). In mammalian cells, including mast cells, there are clear insights to indicate opposite activity patterns among the biosynthetic pathways of both histamine and polyamines (García-Faroldi *et al.*, 2009b). Thus, histamine interferes with both ornithine and spermine uptake systems and is a negative non-direct modulator of ODC activity in mammalian cells (Abrighach *et al.*, 2010; Fajardo *et al.*, 2001a-b). These intertwined regulatory mechanisms are probably part of the molecular coordination of cell proliferation/differentiation programs in mammalian cells. In fact, in mouse bone marrow-derived mast cells, ODC is expressed and the highest spermidine and spermine levels are observed during the initial differentiation stages, in contrast to histamine concentrations (García-Faroldi *et al.*, 2009a).

The antiproliferative role of histamine, in agreement with the observation on transfected HDC overexpressing cells and both the HDC expression profile and histamine production during mast cell differentiation, is apparently in contrast with high HDC expression observed in mast-cell derived malignancies, such as mastocytosis. Valent's group reported that human mastocytosis mast cells display increased expression of HDC and aberrant granules and proposed HDC as a marker of disease malignancy (Krauth *et al.,* 2006). More recently, bone marrow cell hybridomas have also been obtained with high HDC expression (Kawahara, 2012). However, neoplastic cells have severe alterations of their signal transduction mechanisms (such as c-Kit in the case of the most aggressive forms of mastocytosis) (García-Montero *et al.,* 2006), so the behaviour of transformed mast cells with respect to intracellular histamine signalling may be altered compared to normal cells. For instance, in chronic myeloid leukaemia, the oncoprotein BCR/ABL induces HDC expression; of course in these cells, functional properties of some important elements for cell life/death equilibrium are altered (Aichberger *et al.,* 2006). Another possibility associating the survival of neoplastic cells with increased histamine production could be that the neoplastic histamine-producing cells would have higher or new capacities to "hidden" histamine with respect to their normal counterparts. This hypothesis should be pursued since transformed mast cells have altered granule morphologies and histamine (as well as polyamines) can bind to nucleic

acids and has been located in cancer cell nuclei (Medina *et al.,* 2008; Ruiz-Chica *et al.,* 2006).

To our knowledge, there are no pharmacological methods to prevent histamine synthesis by mast cells. Two different inhibitors have been described as substrate analogues and their mechanisms of action have been characterized: monofluoromethyhistidine (alpha-FMH) and histidine methyl ester (HME) (Olmo *et al.,* 2002; Rodríguez-Caso *et al.,* 2003). However, neither can be used clinically. In contrast, the tea polyphenol epigallocatechin 3-gallate (EGCG) has been described as an inhibitor of HDC and DDC. EGCG can inhibit both paralogue enzymes by altering the environment of the cofactor and most probably occluding the catalytic site entrance for the substrate (Ruiz-Pérez *et al.,* 2012). Consequently, these results could be the beginning for development of new preventive and/or therapeutic agents to be used, at least topically, for inflammatory pathologies where mast cell-derived biogenic amines could be an important part of the problem (e.g. prevention of atopic allergy reactions, atopic dermatitis, parasite infections, etc). The antitumourigenic and anti-inflammatory properties described for EGCG (as an inhibitor of angiogenesis and NF-κB signalling) suggest that EGCG or its derivatives may be promising drugs against mastocytosis (Melgarejo *et al.,* 2007, 2009 and 2010 a and b). Other rare diseases could also benefit from the development of new histamine synthesis modulators (Pino-Ángeles *et al.,* 2012).

An overview of the interactions between histamine, polyamines and various cell types is given in Figure 4.2. Histamine can have autocrine effects on mast cells usually *via* the H_1R and H_4R. Modulation of the activity of these receptors to discover new and more effective anti-inflammatory strategies is also an active field of R&D (Ohsawa & Hirasawa, 2012). It is the subject of other chapters/subsections of this volume.

4.2.3. Action of Histamine on Mast Cells and Basophils

In 1953, Riley & West reported for the first time that the major storage site of histamine in mammalian tissues was located in the mast cells (Riley & West, 1953), usually in the cells' secretory granules. Mast cells not only release histamine upon activation through FcεRI but also via other stimuli such as cytotoxic agents, polysaccharides, lectins, anaphylatoxins, calcium and many basic compounds (such as compound 48/80) (Lagunoff, Martin, & Read, 1983). Eosinophils can also activate the mast cells to release histamine (Piliponsky *et al.,* 1999). Histamine can act both in stimulatory and inhibitory ways on immune cells; it can enhance the antigen-presentation by dendritic cells, suppress TNF-α and IL-12 and increase IL-10 production by dendritic cells and monocytes (Hsu & Boyce, 2009). Recently, histamine has been reported to induce neuronal hypertrophy and increase the mast cell density in the gastrointestinal tract

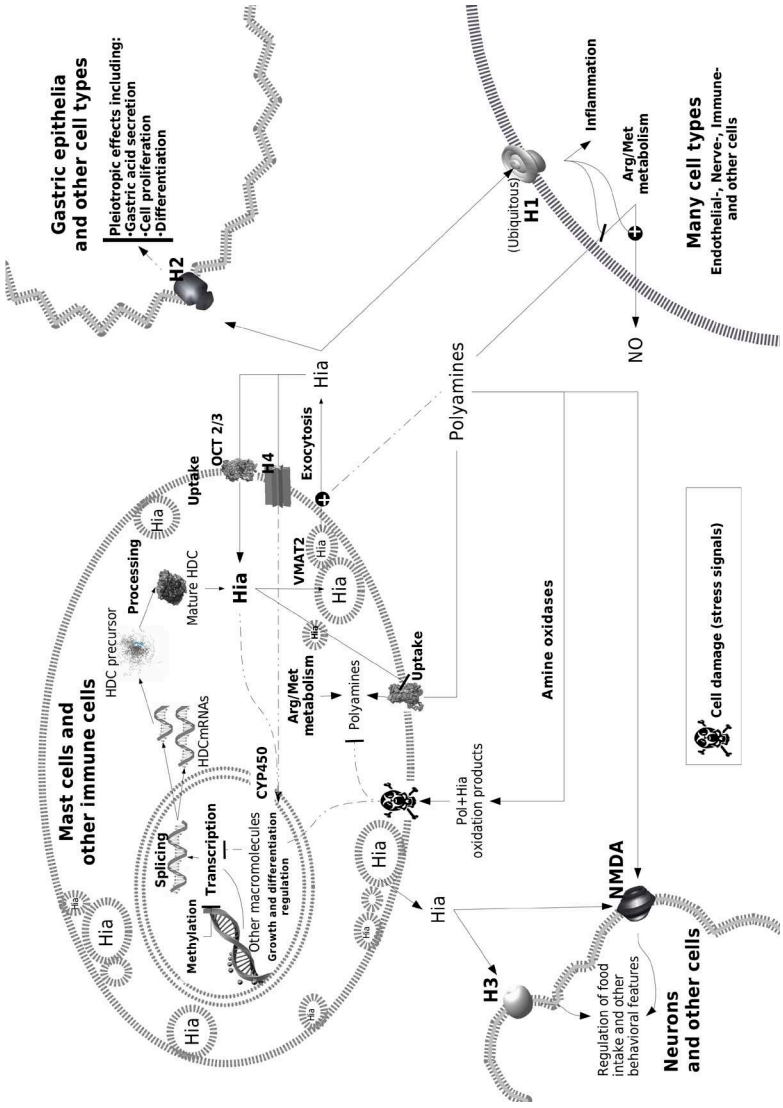

Figure 4.2 Effects of histamine on different cell types
Abbreviations: CYP450: cytochrome P450; Hia: histamine; H_{1-4}: histamine receptor 1-4 subtype; NMDA: N-methyl-D-aspartate receptor; NO: nitrogen oxide; OCT 2/3: organic cation transporter 2/3; Pol: polyamines; VMAT2: vesicular monoamine transporter2

(Keles *et al.,* 2012). Histamine modulates cell events and plays an important role in immune modulation and allergic inflammation through histamine receptors (Table 4.1). Histamine acts through these receptors to mediate effects that include vasodilation and vasopermeability, smooth muscle contraction of bronchial and gastrointestinal tract, secretion of gastric acid, and induction of pruritus (Jutel, Blaser, & Akdis, 2005).

Despite being the major producers and releasers of histamine, it has long been appreciated that mast cells and basophils are also affected by an autocrine action of the amine, which may play an important role in limiting their ability to further degranulate (Bourne *et al.,* 1971; Lippert *et al.,* 2004). However, owing to the difficulty in obtaining and purifying isolated primary human mast cells and basophils, a comprehensive analysis of HR expression (H_1-4R) has not yet been completed in these cells. Despite this, much of the feedback inhibition in basophils and human skin mast cells is thought to be H_2R-mediated (Lichtenstein & Gillespie 1973) although less is known regarding human lung mast cells or other mast cell types, which often display a marked degree of functional heterogeneity (Peters *et al.*, 1982, MacGlashan, 2003).

H_2R agonists (such as impromidine) but not H_1R agonists mimic the inhibitory actions of histamine on mast cells activated by compound 48/80 (an IgE-independent stimulus) and are reversed by the H_2R antagonist cimetidine (Masini *et al.,* 1982). However, the H_2R-mediated inhibitory actions of histamine caused by IgE-dependent activation, seem to be more prominent in basophils than mast cells (Kazimierczak *et al.,* 1981; Summers *et al.,* 1981; Peters *et al.,* 1982). Recently, it was reported that this receptor is involved in the early suppression of basophils to release all known major mediator classes during venom-allergen immunotherapy (Novak *et al.,* 2012). The mechanism responsible for H_2R-mediated inhibition of basophil activation is due to elevation of cyclic AMP and subsequent inhibition of extracellular calcium influx into these cells (Botana & MacGlashan, 1994; Lippert *et al.,* 2004).

Table 4.1
Effects of histamine through its specific receptors on mast cells and eosinophils.

Receptor	Mast cell	Eosinophil
H_1R	Activation ↑, IP3/[Ca^{2+}] ↑	Chemotaxis ↑
H_2R	Chemotaxis ↓	$fMLPO_2^-$ production ↓ IL-4 mediated inflammation ↑
H_3R	Expressed in brain mast cell Auto-receptor	Chemotaxis ↑*
H_4R	Chemotaxis ↑, cAMP ↑, [Ca^{2+}] mobilization	Cell shape change chemotaxis ↑, CD11b ↑, CD54 ↑

* controversial, ↑ increase, ↓ decrease

H_1R-antagonists also lead to increased intracellular cAMP generation due to competitive antagonism with H_2R (Palacios *et al.,* 1978; Lippert, *et al.,* 2004) and some more recent generation H_1R antagonists can reduce mast cell function (Levi-Schaffer, 2009). However, H_1R expression in these mast cells and basophils is relatively low, although there is tentative evidence to suggest that it may be higher in immature mast cells (Lippert *et al.,* 2004) and guinea pig basophils, where this receptor is involved in histidine uptake (Stewart & Kay, 1980). In a mouse model of allergen-induced pulmonary inflammation, H_1R was found to have a key role in T cell chemotaxis (Bryce *et al.,* 2006). It also increases the Th1 type of cellular immune response and IFN-γ production. However, H_1R decreased the IgE production (Simons & Akdis, 2009).

Certain H_1R antagonists such as terfenadine (but not cetirizine) can inhibit IgE-dependent mediator release from basophils (Gibbs *et al.,* 1998) but only at high concentrations (μM range) and it is unlikely that these effects are H_1R specific. Nevertheless, new generation H_1R antagonists are used as anti-allergic/mast cell stabilizing drugs due to their ability to inhibit mast cell activation (Levi-Schaffer & Eliashar, 2009), even though some of them might increase cellular cAMP in competitive antagonism with H_2R. It has become increasingly apparent that species differences in histamine receptor isoforms may considerably impact on the agonist-antagonist pharmacology of various $H_{1\text{-}4}$R modulating agents, their potency as well as their specificity to a particular HR type (Schnell *et al.,* 2011; Seifert *et al.,* 2003; Seifert *et al.,* 2011).

The H_3R is expressed in brain mast cells but there have been conflicting reports regarding the actions of H_3R modulators on peripheral tissue mast cells (Bissonnette, 1996; Nemmar *et al.,* 1999; Rozniecki *et al.,* 1999). In basophils, the H_3R does not appear to affect function (Kleine-Tebbe *et al.,* 1990; Tedeschi *et al.,* 1991). These reports may reflect the problem associated with the 40% sequence homology of H_3R with H_4R (Liu *et al.,* 2001; Morse *et al.,* 2001) where agents such as α-methylhistamine (agonist) and thioperamide (antagonist) affect both receptor types.

Lippert *et al.* showed that H_3R is not expressed on human skin mast cells, in contrast to high levels of H_4R expression (Lippert *et al.,* 2004). Basophils also express H_4R (Hofstra *et al.,* 2003) but, as with human mast cells, there are no data at present to indicate a major role for this receptor in controlling mediator release from human mast cells and basophils. In mice, chemotaxis, intracellular calcium mobilization and LTB_4 have been shown to be affected by H_4R triggering, though degranulation and cAMP changes are not directly affected (Hofstra *et al.,* 2003; Rosethorne & Charlton, 2011; Takeshita *et al.,* 2003; Godot *et al.,* 2007). Even though H_4R has not been shown to substantially affect mast cell and basophil mediator release, it is thought to play a role in effector cell (such as eosinophil) recruitment to tissues affected by chronic allergic inflammation (Hofstra *et al.,* 2003). H_4R was also shown to control human mast cell precursor

trafficking in the presence of CXCL12 (Godot, *et al.,* 2007) and regulate the migration of mast cells and eosinophils into guinea pig airway epithelial tissue after allergen challenge (Yu *et al.,* 2008). It would be of considerable interest if a reduction in mast cell numbers within tissues affected by allergic inflammation were demonstrated in humans due to a suppression of H_4R-mediated trafficking of mast cells and their precursors, especially given the other properties H_4R antagonists/inverse agonists on suppressing histamine-related itch (Ohsawa & Hirasawa, 2012). However, the species differences in HR isoforms and the pharmacological effects of various HR-modulating agents may be a major obstacle in the rapid development of new H_4R–blocking drugs.

4.3. Eosinophils

Eosinophils are blood-borne granulocytes that migrate into tissues in some physiological and pathological conditions where they survive for several days. Eosinophils are generated from myeloid progenitor cells in the bone marrow. The differentiation of myeloid progenitor cells into mature eosinophils requires critical transcription factors, namely GATA-1[2], PU.1[3] and C/EBP[4] (McNagny & Graf, 2002; Nerlov & Graf, 1998; Nerlov *et al.,* 1998). The development and proliferation of eosinophils is positively regulated by granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as IL-3 and IL-5 cytokines (Lopez *et al.,* 1986; Lopez *et al.,* 1988; Rothenberg *et al.,* 1988; Takatsu, Takaki, & Hitoshi, 1994). Eosinophils consist of a characteristic bilobed nucleus and a cytoplasm enriched in secondary granules, which contain major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN). These cationic proteins are cytotoxic molecules that play an important role in inflammation, allergy, parasitic infection, tissue injury and tumors. Eosinophil cytoplasm also contains other 'granule' types, namely: small granules, primary granules, lipid bodies and small secretory vesicles. Eosinophils respond to diverse stimuli by degranulating and releasing these cationic proteins, lipid mediators, cytokines, chemokines, and neuromodulators (Gleich & Adolphson, 1986). Eosinophils express various cell surface markers, such as Fc receptors, CCR3, PAF receptors, CD48, 2B4, Siglec-F and histamine receptors, which are responsible for cell-cell communication via various pathways. These receptors are grouped into adhesion molecules, cytokine

2 A zinc family finger member
3 An ETS family member
4 CCAAT/enhancer-binding protein family

receptors, immunoglobulin receptors and members of the immunoglobulin superfamily, chemotactic factors, enzymes, and molecules associated with apoptosis and cellular signalling (Rothenberg & Hogan, 2006).

4.3.1. Function of Eosinophils

Eosinophils have many functions (Figure 4.3) associated with the pathogenesis of various inflammatory diseases including parasitic helminth infections (Wardlaw & Moqbel, 1992;Weller, 1994), intestinal immunity (Hogan, Waddell, & Fulkerson, 2012), allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, etc. (Weller, 2009) and they can function as antigen presenting cells (APCs) since they can both process and present a variety of microbial, viral, and parasitic antigens (Shi, 2004). Eosinophils secrete various cytokines capable of promoting T-cell proliferation, activation and Th1/Th2 polarization. Murine eosinophils promote the secretion of IL-4, IL-5 and IL-13 cytokines by

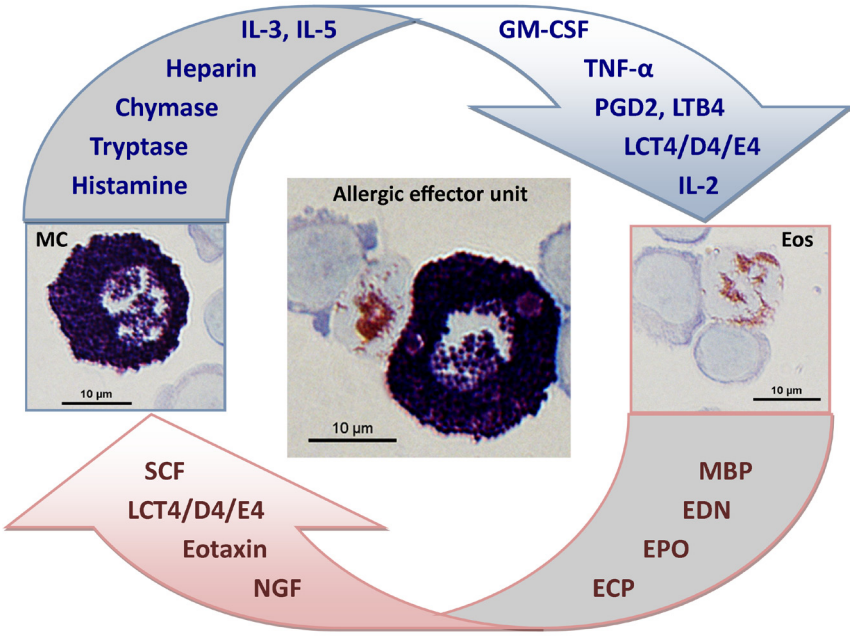

Figure 4.3 Soluble and physical interactions between mast cells and eosinophils. In this illustrative diagram, soluble interactions have been shown by boxed arrows with some of the key mediators secreted by mast cells and eosinophils responsible for mediating soluble interactions between them. At the centre, the allergic effector unit showing physical interaction between eosinophils and mast cells.

$CD4^+$ T-cells (MacKenzie *et al.,* 2001). Human eosinophils also produce nerve growth factor (NGF), which is required for survival and functional maintenance of sympathetic neurons and also regulates immune responses (Solomon et al., 1998). However the antigen presenting capacity of eosinophils is a controversial subject (van Rijt *et al.,* 2003) as reviewed in (Rothenberg & Hogan, 2006).

4.3.2. Action of Histamine on Eosinophils

Mast cells together with eosinophils, form "the allergic effector unit" (Figure 4.3), that is considered to be the basic functional unit of allergy. Eosinophils and mast cells communicate with each other in a bidirectional manner. This interaction is both physical through cell surface receptors such as CD48, 2B4 (Elishmereni *et al.,* 2011; Minai-Fleminger *et al.,* 2010) and/or soluble through various cytokines and chemokines (Minai-Fleminger & Levi-Schaffer, 2009) (Figure 4.3). Eosinophils can regulate mast cell function and *vice versa.* Eosinophil MBP can activate human umbilical cord blood–derived mast cells to release histamine, IL-8, GM-CSF, PGD-2, and TNF-α (Piliponsky *et al.,* 2002). The mast cell protease chymase activates eosinophils and promotes the production of SCF. Eosinophil released NGF promotes mast cell survival and activation (Bullock & Johnson, 1996; Horigome, Bullock, & Johnson, 1994). NGF also acts in an autocrine manner by activating the release of EPO (Solomon *et al.,* 1998). EPO activates rat peritoneal mast cells to release histamine. The release of histamine occurs in a dose dependent manner upon incubation with MBP, EPO, and ECP (Zheutlin *et al.,* 1984). Histamine can promote superoxide (O_2^-) production in eosinophils which enhances the expression of C3b receptor and other membrane receptors (Pincus, DiNapoli, & Schooley, 1982).

Overall, histamine influences eosinophil cell shape, upregulates the expression of adhesion molecules (CD11b and CD54) and induces chemotaxis (Ling *et al.,* 2004). Histamine-induced eosinophil chemotaxis is blocked by the H_4 receptor antagonist JNJ 7777120 and the H_3/H_4 receptor antagonist thioperamide, but not by H_1 (diphenhydramine), H_2 (ranitidine) or H_3 receptor antagonists (Ling *et al.,* 2004). Moreover, selective H_1R- and H_2R agonists do not mimic the effects of histamine. In contrast, H_2R plays an inhibitory role in the activation of chemotaxis. Intriguingly, there is no inhibitory impact of H_2R on the regulation of intracellular calcium Ca^{2+} concentrations, indicating that chemotaxis is regulated independently of rises in intracellular Ca^{2+} levels (Reher *et al.,* 2012).

Synergy between histamine- and IL-4-mediated recruitment of eosinophils to the lung has been reported, as histamine is necessary to generate IL-4-driven eosinophilic inflammation, mediated via H_2R. Additionally, alveolar epithelial cells require H_2R to produce CCL24, an eosinophil recruitment factor (Swartzendruber, Byrne, & Bryce, 2012). Allergic asthma was induced in the

histidine decarboxylase deficient mouse model and it was found that histamine positively controls eosinophilia (mediated by H_4 receptor) but not bronchial hypersensitivity (Ohtsu, 2010). In a mouse model of asthma, H_4R was found to influence the induction of Th2 responses by dendritic cells (Dunford *et al.,* 2006) and may play a role in mediating pruritus (Dunford *et al.,* 2007).

Based on these results, an effective treatment of allergy should be developed as a combinational therapy that targets not only H_1R but the other receptors as well, especially H_4R. This kind of therapy can interfere with both mast cells and eosinophils and reduce the overall allergic inflammation.

4.4. Monocytes and Macrophages

The mononuclear phagocytic system is generated from committed haematopoietic stem cells located in the bone marrow (Murray & Wynn, 2011). Monocytes released from bone marrow into the circulation that can further differentiate into a range of tissue macrophages and dendritic cells (Fogg *et al.,* 2006; Hume *et al.,* 2002; Shi & Pamer, 2011). Bloodstream monocytes are subdivided into subsets that differ in size, trafficking and innate immune receptor expression and in their ability to differentiate following stimulation with cytokines and/or microbial molecules (Auffray *et al.,* 2009; Geissmann *et al.,* 2003). Monocytes mediate host antimicrobial defence (Serbina *et al.,* 2008) and are also implicated in many inflammatory diseases (Woollard & Geissmann, 2010). Although several subsets of monocytes and macrophages have been identified, the individual contributions of these subsets to health and disease are not well known, and it is probable that additional, functionally distinct subsets exist (Chow *et al.,* 2011).

4.4.1. Function of Monocytes/Macrophages

When monocytes migrate from the circulation and extravasate through the endothelium, they differentiate into macrophages or dendritic cells (Murray & Wynn, 2011). Thus, the primary role of monocytes is to replenish the pool of tissue-resident macrophages and dendritic cells in steady state and in response to inflammation. Monocytes, dendritic cells and macrophages, along with neutrophils and mast cells, are 'professional' phagocytic cells which express a multitude of receptors on their surfaces that detect signals that are not normally found in healthy tissues. An initial level of macrophage activation occurs when early warning signals trigger monocyte recruitment and *in situ* activation, or when IL-4 induces *in situ* macrophage proliferation (Jenkins *et al.,* 2011). Tissue damage sensing is probably crucial at the second level of macrophage response, regardless of whether the damage is of a microbial nature. The mechanisms of tissue damage sensing have been discussed in recent reviews (Chen & Nunez,

2010; Matzinger & Kamala, 2011). Beyond the initial activation and stimulation of macrophages, cooperative actions of multiple sensors, feed forward cytokine networks and inter-organ communication increase the output of monocytes and neutrophils driving inflammatory responses. Macrophage effectors work together in cell-intrinsic and cell-extrinsic networks (Nish & Medzhitov, 2011). For example, the production of interferon-γ (IFNγ) by T helper 1 (Th1) cells requires IL-12 production from activated mononuclear phagocytes, where IFNγ then stimulates macrophages to activate the antimicrobial mechanisms (Borden *et al.,* 2007).

The activation of mononuclear phagocytes leads to the generation of the superoxide anion radical and nitric oxide (NO) by NADPH oxidase as well as inducible nitric oxide synthase (iNOS), respectively (Ambrozova *et al.,* 2010; Ambrozova *et al.,* 2011). Both the superoxide anion radical and nitric oxide generate secondary reactive oxygen species (ROS) and reactive nitrogen species (RNS). Physiologically, ROS and RNS formation is one of the essential microbicidal mechanisms in the body. Although formation of reactive species is desirable for host defence, their overproduction can cause damage to the body's own cells and tissue injury can contribute to the development of a number of serious diseases. Thus, the modulation of their production is an important target in the treatment of immune and inflammatory diseases (Lojek *et al.,* 2008; Ren & Chung, 2007).

A key component of the macrophage response is also the production of anti-inflammatory feedback mechanisms that encompass cell-intrinsic signalling feedback loops and cell-extrinsic mechanisms, such as the production of IL-10, which is an essential and non-redundant anti-inflammatory cytokine (Murray & Wynn, 2011). This part of macrophage response is the least clear and involves the final balance between chronic inflammation and re-establishment of homeostasis. The understanding of the underlying mechanisms that restore homeostasis after an inflammatory reaction underpins all research efforts related to chronic inflammatory diseases.

4.4.2. Action of Histamine on Monocytes/Macrophages

Histamine via H_1R, H_2R, H_3R, and H_4R has both proinflammatory or anti-inflammatory effects, depending on the predominance of the types of histamine receptors (Tripathi *et al.,* 2010) and histamine concentration. Histamine stimulates the release of proinflammatory cytokines and lysosomal enzymes from human macrophages.

Khan and Rai (Khan & Rai, 2007) reported that histamine differentially regulated the testicular macrophage immune responses in wall lizards. It inhibited phagocytosis and superoxide production at high concentrations (10^{-5} M) while it stimulated superoxide production and did not affect phagocytosis at low

concentrations (10^{-10} M). Using selective H_1R and H_2R antagonists, pyrilamine and famotidine respectively, the H_1R subtype was responsible for mediating the inhibitory effect of histamine on testicular macrophage immune responses at high concentrations, while H_2R were involved in the stimulation at low concentrations. In contrast, Azuma and co-workers (Azuma *et al.,* 2001) found that *in vitro* treatment of macrophages with histamine resulted in inhibition of chemotaxis and histamine at 10^{-5} M markedly inhibited the production of superoxide anions from both opsonized zymosan-A and phorbol 12-myristate 13-acetate stimulated macrophages. Furthermore, histamine at a concentration range of 10^{-7} to 10^{-5} M significantly inhibited phagocytosis of *Escherichia coli* by macrophages. In addition, the H_2R-selective agonist dimaprit resulted in inhibition of macrophage chemotaxis and markedly inhibited the production of superoxide anion by phorbol 12-myristate 13-acetate-stimulated macrophages and phagocytosis of *E. coli* by macrophages. In contrast, both histamine and dimaprit caused a concentration-dependent inhibition of lipopolysaccharide-induced production of TNFα and IL-12 by macrophages. These results suggest that histamine and dimaprit may inhibit chemotaxis, phagocytosis, superoxide anion production and the production of TNFα and IL-12 by macrophages via the histamine H_2R.

Monocytes and tissue macrophages exhibit different responses to histamine treatment, indicating that differentiation of monocytes to tissue macrophages might induce changes in the expression of H_1R. Triggiani and co-workers (Triggiani *et al.,* 2007) found that human lung macrophages had a higher expression of H_1R mRNA and protein than monocytes. Moreover, they found high protein expression of H_1R in monocyte-derived macrophages in contrast to the nearly undetectable expression of this protein in monocytes. Simultaneous analysis of H_2R and H_1R mRNA expression indicated that the H_2R/H_1R ratio is approximately 100-fold higher in monocytes in comparison with monocyte-derived macrophages. Similarly, a shift from H_2R to H_1R during differentiation of histiocytic lymphoma cells U937 and human peripheral blood monocytes into macrophages was also reported (Wang *et al.,* 2000). U937 cells are widely used as a model for monocytes. Differentiation of these cells increased H_1R expression and decreased the H_2R expression. These effects may be explained by the results of Murata and coworkers (Murata *et al.,* 2005), who found H_2R mRNA in U937 cells is constitutively expressed and does not react to GM-CSF. In contrast, GM-CSF increased mRNA expression for H_1R. These U937 cells do not express H_3R (Wang *et al.,* 2000). Spontaneous and retinoic acid-induced differentiation of normal human monocytes and of leukemic THP-1 monocytes into macrophages results in a progressive loss of adenosine 3',5'-cyclic monophosphate production induced by histamine via H_2R (Mirossay *et al.,* 1994). In THP-1 cells and in HL-60 cells, retinoic acid treatment increased the abundance of mRNA expression of the H_2R gene 4-fold, suggesting transcriptional control by a retinoic acid response

element. In THP-1 macrophages, histamine inhibited phorbol 12-myristate 13-acetate-induced H_2O_2 formation via the activation of H_2R. Expression of the H_2R gene, histamine accumulation, and histidine decarboxylase activity were also demonstrated in normal human monocytes/macrophages and peripheral lymphocytes.

Vignola and coworkers (Vignola *et al.,* 1994) found that histamine induced a significant increase in alveolar macrophages expressing the LFA-1, ICAM-1 and CD23b membrane markers and a significant increase in the release of fibronectin. The histamine effects were H_1R specific, since they were significantly inhibited by an H_1R antagonist pyrilamine. In contrast, Sirois and co-workers found that when alveolar macrophages from humans, Sprague Dawley rats and the rat alveolar macrophage cell line NR8383 were treated with histamine prior to their stimulation with lipopolysaccharide, histamine inhibited lipopolysaccharide-stimulated TNF release in a dose-dependent manner (Sirois *et al.,* 2000). This inhibition was mimicked by H_2R and H_3R agonists, but not by the H_1R agonist betahistine. Furthermore, these authors reported the expression of H_3R mRNA in human alveolar macrophages. Other authors (Morichika *et al.,* 2003; Takahashi *et al.,* 2002) found that histamine inhibited CD14, ICAM-1 and CD80 expression on human peripheral blood mononuclear cells induced by lipopolysaccharide and IL-18, respectively. TLR stimulation of monocytes is altered by histamine co-incubation as secretion of pro-inflammatory cytokines such as TNFα, IL-12 and IL-18 is suppressed, while IL-10 secretion is enhanced. The modulatory effects of histamine on ICAM-1 expression and cytokine production were antagonized by the H_2R antagonist famotidine but not by d-chlorpheniramine and thioperamide, and were mimicked by selective H_2R agonists but not by H_1R, H_3R and H_4R agonists, indicating the involvement of the H_2R in the action of histamine (Takahashi *et al.,* 2002, 2004; Morichika, *et al.,* 2003). Monocytes stimulated by advanced glycation end products are known to up-regulate adhesion molecule expression but this effect is inhibited by the H_2R (Zhang *et al.,* 2010). Using THP-1 cells, Tanimoto and colleagues (Tanimoto *et al.,* 2001) showed that H_1R and H_2R mRNA were present in non-differentiated monocytic THP-1 cells, whereas in TPA-differentiated THP-1 macrophages, mRNA encoding for H_1R, H_2R and H_4R (very low) was present. Nevertheless, the H_1R and H_2R mRNA were the most abundant. The monocytic THP-1 cells expressed higher amounts of H_2R mRNA than H_1R mRNA in comparison with differentiated THP-1 cells.

Dijkstra and co-workers (Dijkstra *et al.,* 2007) showed the expression of H_4R in human monocytes obtained from peripheral blood by using flow cytometry. The expression of H_4R was increased by IFN-γ. Histamine and H_4R agonists (clobenpropit and 4-methylhistamine) induced calcium mobilization in monocytes. These effects were blocked by H_4R antagonist JNJ7777120. In contrast, these agonists inhibited production of CCL2 by monocytes. Supernatants of H_4R agonist-stimulated monocytes attracted fewer monocytes in transmigration assays,

resulting in a reduction of monocyte recruitment. Damaj and colleagues (Damaj *et al.,* 2007) described the protein expression of H_4R in human monocytic cell lines THP-1, U937 and human peripheral blood monocytes using flow cytometry or immunoblot assays. Their results showed much lower expression of H_4R in peripheral blood monocytes. Ohki and co-workers (Ohki *et al.,* 2007) showed co-expression of H_4R with macrophage markers CD68 and CD163 in macrophage-like cells from the human synovial tissues of patients with rheumatoid arthritis. Recently, Gschwandtner and colleagues (Gschwandtner *et al.,* 2013) reported that several H_4R agonists reduced the secretion of IL-12p70 from monocytes but the EC_{50} values were lower than those obtained with pharmacological assays.

From the available data, it is clear that histamine modulates macrophage/monocyte activity and their physiological/pathophysiological effects. It remains to be clarified which effects are receptor mediated and which histamine receptors are involved in histamine effects on macrophages.

4.5. Dendritic Cells

Dendritic cells are potent antigen-presenting cells that are present throughout the body and are central players in initiating and regulating innate and adaptive immune responses, particularly at mucosal sites. Dendritic cell survival, activation, maturation and polarization are largely influenced by local factors within their micro-environment such as microbial components, cytokines and metabolic products. Dendritic cells shape the functional polarization and differentiation of the reactive T-cells into Th1, Th2, Th9, Th17 and T_{reg} responses by producing cytokines such as IL-12, IL-18, IL-23, IL-11, IL-10 or TGFß (Akdis *et al.,* 2011). The selection of an appropriate cytokine secretion pattern by dendritic cells is dependent on a number of factors, but is particularly influenced by the binding of microbial ligands, termed pathogen-associated molecular patterns (PAMPs), to pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) and C-type lectin receptors (CLRs) (O'Mahony *et al.,* 2006; Shilling *et al.,* 2007). Dendritic cells are often found in close proximity to degranulated mast cells and can secrete histamine following activation under certain conditions.

4.5.1. Action of Histamine on Dendritic Cells

While dendritic cells have been shown to express H_1R, H_2R and H_4R, it is not definitively established if the level of HR expression is altered during maturation or if different dendritic cell subsets (e.g. myeloid or plasmacytoid dendritic cells) preferentially up- or down-regulate individual HRs following specific micro-environmental cues. Dendritic cells exposed to histamine have been shown to up-regulate their antigen-presenting capacity and Th1 polarization via the H_1R

while activation of the H_2R on dendritic cells preferentially drives IL-10 secretion and, under certain circumstances, promotes Th2 polarisation (Caron *et al.,* 2001; Mazzoni *et al.,* 2001; van der Pouw Kraan *et al.,* 1998). H_2R activation of human plasmacytoid dendritic cells leads to a significant down-regulation of IFNγ and TNFα secretion following CpG stimulation (Mazzoni *et al.,* 2003). In addition, accumulation of plasmacytoid dendritic cells and $CD11b^+$ dendritic cells, but not $CD8^+$ dendritic cells, in draining lymph nodes is H_2R dependent (Dawicki *et al.,* 2010). Furthermore, histamine reduces the production of NADPH-oxidase-derived oxygen radicals by several types of myeloid cells, an effect mediated by the H_2R (Hellstrand *et al.*, 1994). However, Gschwandtner *et al.,* (2011) found that human plasmacytoid dendritic cells from patients with psoriasis had high levels of the H_4R compared to controls or those from atopic dermatitis patients. Histamine treatment reduced cytokine production from these cells and was more marked in those from patients with psoriasis.

In contrast to other dendritic cell subsets, Langerhans cells within the epidermis seem to be regulated uniquely by histamine as they do not express H_1R or H_2R (Ohtani *et al.,* 2003). However, Langerhans cells do express H_4R and human inflammatory dendritic epidermal cells can express H_4R following exposure to IFNγ, which results in the downregulation of CCL2 and IL-12 secretion in an H_4R-dependent mechanism (Gschwandtner *et al.,* 2010; Dijkstra, *et al.,* 2008). In contrast, murine studies suggest that inhibition of H_4R on dendritic cells leads to decreased cytokine and chemokine production, which limits their ability to induce Th2 responses. Simon *et al.*, 2011 found an increased antigen presentation capacity in dendritic cells from $H_4R^{-/-}$ mice. These mice had reduced mRNA expression of cytokines such as IFNγ and IL-10. Recently, dendritic cell H_1R expression was shown to be required for IFNγ production by CD8 cells resulting in atopic dermatitis in a murine model (Vanbervliet *et al.,* 2011). Interestingly, $IL\text{-}17^+CD8$ cells were induced by dendritic cells lacking H_1R. Certain bacterial strains present within the human diet express the HDC gene and have been shown to release histamine (Coton *et al.,* 2010). However, the *in vivo* homeostatic consequences of histamine release by these bacteria has not yet been determined, although it is likely that histamine-producing bacteria could impact the dendritic cell response to the bacteria itself and other bacterial strains through a bystander effect.

Due to their potent ability to influence innate activation and adaptive polarization, dendritic cells are key cellular players in orchestrating protective and tolerogenic immune responses. Inappropriate dendritic cell PRR signalling has been associated with multiple inflammatory diseases, particularly those of tissues exposed to the external environment such as the gastrointestinal tract, the lungs and the skin. Histamine and its four receptors represent a complex system of immunoregulation with distinct dendritic cell effects dependent on receptor subtype expression (O'Mahony *et al.,* 2011). Strategies that promote dendritic

cell H_2R expression and activity could improve mucosal immuoregulatory activity and protect against allergic sensitization and inflammatory disorders.

4.6. Polymorphonuclear Neutrophils

Polymorphonuclear neutrophils (or neutrophils) are the most abundant leukocytes in blood and constitute the first line of defence against bacteria and fungi. During episodes of infection, neutrophils leave the blood circulation and migrate to inflamed tissues (extravasation) where they clear the pathogens by a process called phagocytosis. The recruitment of neutrophils to sites of inflammation is a complex process orchestrated by soluble mediators (formyl peptides, chemokines, pro-inflammatory cytokines, complement split products) and adhesion receptors (selectins and β2 integrins) (Ley *et al.*, 2007). The soluble mediators, which are produced during episodes of infection, induce expression of β2 integrins on the membrane surface of neutrophils (Sengeløv, 1993), the main adhesion receptors expressed in neutrophils. The soluble mediators also switch the β2 integrins from a low to a high affinity ligand binding conformation (inside-out signalling) (Diamond & Springer, 1993). This change of conformation in β2 integrins is required for strong attachment to the endothelium, migration along the endothelial layer and the subsequent transendothelial migration. In infected tissues, neutrophils migrate towards the pathogens and capture them. The capture of opsonised microorganisms primarily involves two receptors: the β2 integrins and the Fcγ receptors. The microoganisms are trapped inside the phagosome, which fuses with intracellular granules. The release of the granule content (proteases and anti-microbial peptides) into the phagosome, coupled with the production of reactive oxygen species, is responsible for the destruction of the microorganisms (Sheppard *et al.*, 2005).

4.6.1. Action of Histamine on Neutrophils

Histamine H_1 binding sites are present in human neutrophils (Wescott & Kaliner, 1983). [^{3}H]pyrilamine, an H_1R antagonist, binds human neutrophils in a specific, saturable and reversible fashion. Furthermore, the binding of [^{3}H]pyrilamine is competed (by order of potency) by H_1 antagonists, histamine, and H_2 antagonists. It was estimated that human neutrophils express a large number of H_1R (265 x 10^3/cell) and have a homogeneous population of H_1R, with a moderate affinity for histamine (K_D = 52 nM). Another study reported presence of H_2- but not H_1-binding sites in neutrophils. A bioactive fluorescent derivative of histamine was shown to bind to the membrane surface of human neutrophils and histamine, cimetidine (an H_2R antagonist) but not diphenhydramine (H_1R antagonist) competed with the fluorescent derivative of histamine for binding sites (Petty & Francis, 1986).

Little information is available regarding expression of histamine receptors in neutrophils. There is a lack of information regarding expression of H_1R, H_2R or H_3R in neutrophils. There is controversy as to whether the H_4R is present in human neutrophils. The mRNA encoding for H_4R was found in human neutrophils (Oda *et al.,* 2000; Zhu *et al.,* 2001) and in HL-60 cells differentiated into granulocytes (Van Rijn *et al.,* 2006). However, other investigators did not detect the H_4R messenger RNA in neutrophils (Ling *et al.,* 2004).

There is consistent support for a role of histamine in the inhibition of antimicrobial functions of human neutrophils. Histamine inhibits neutrophil degranulation induced by the potent chemoattractant fMLP (Seligmann *et al.,* 1983; Burde *et al.,* 1989) or by zymosan particles (Busse & Sosman, 1976). Histamine also blunts fMLP-induced superoxide production in neutrophils (Seligmann *et al.,* 1983; Burde *et al.,* 1989). These effects of histamine are mediated by H_2R but not by H_1R. Indeed, antagonists of H_2R such as metiamide (Busse & Sosman, 1976), cimetidine (Seligmann *et al.,* 1983), ranitidine (Zimmerman & Millard, 1989) and famotidine (Burde *et al.,* 1989) prevented these inhibitory effects of histamine. In contrast, chlorpheniramine, an antagonist of the H_1R did not prevent histamine blocking degranulation induced by zymosan particles (Busse & Sosman, 1976). Additional evidence for the involvement of H_2R in the negative regulation of neutrophil functions is provided by studies showing that inhibition of neutrophil degranulation by histamine is also reproduced by guanidine-type H_2-agonists structurally derived from impromidine (Burde *et al.,* 1989). The regulatory effect of the H_2R on neutrophil functions may be mediated through activation of adenylyl cyclase and increased production of the second messenger cAMP (Burde *et al.,* 1989; Busse & Sosman, 1976). It remains to be investigated whether the H_4R plays a role in the regulation of neutrophil antimicrobial functions.

Neutrophils stimulated with fMLP synthesize and release leukotrienes which are potent chemoattractants for neutrophils. Furthermore, histamine blocks fMLP-induced production of leukotrienes (Flamand *et al.,* 2004). It is therefore plausible that the ability of histamine to block neutrophil functions is due to reduced synthesis of potent activators of neutrophil functions. Based on the use of pharmacological antagonists of H_2R (cimetidine, ranitidine, and tiotidine) and H_4R (thioperamide), it has been shown that H_2R but not H_4R is involved in the inhibition of fMLP-induced biosynthesis of leukotrienes by histamine (Flamand *et al.,* 2004). Histamine also has profound effects on the oxidative burst and release of reactive oxygen species from neutrophils; however, these observations could be considered controversial (for full discussion see: Cíž & Lojek, 2013).

In addition to its regulatory role of antimicrobial functions, histamine has been demonstrated to regulate neutrophil adhesion and chemotaxis. Histamine caused limited inhibition of fMLP-dependent chemotaxis while stimulating chemokinesis (Seligmann *et al.,* 1983). The ability of histamine to prevent chemotaxis may be

explained by the fact that the vasoamine diminishes expression of β2 integrins on the membrane surface (Francis *et al.,* 1991). In contrast, by using a mouse mast-cell-dependent model of zymosan-induced peritonitis, it was proposed that histamine, by acting on H_4R, controls neutrophil chemotaxis. Indeed, the H_4R antagonist A-940894 blocks neutrophil influx in the peritoneum (Strakhova *et al.*, 2009). However, the H_4R may indirectly control neutrophil migration by regulating expression levels of chemoattactants and chemokines.

Histamine could play a key role in the resolution of inflammation. Indeed, in response to engagement of the TLR 4 (which binds gram negative bacteria), neutrophils produce histamine (Smuda *et al.,* 2011). When pathogens have been cleared, histamine could limit neutrophil degranulation and reactive oxygen species production in order to avoid tissue damage.

4.7. Conclusions

The role of histamine in allergic reactions is undisputed. However, our increasing knowledge about this mediator and its functions places it central stage in the orchestration of the innate immune response and leading to the adaptive response. Studies have been complicated because of the differences in the receptors between species. Cellular responses also vary depending on the original tissue from which the cells were isolated, which is of special relevance for mast cells. The movement of cells from the blood stream out into the tissues, airways or gut can also modulate the expression of receptors and receptor subtypes. Finally an area that has received less attention, the underlying disease state may also cause modifications to receptor expression and/or the response to stimuli.

From the data presented above, further work is necessary to elucidate the different HRs on inflammatory cells such as basophils, mast cells and neutrophils. The complex interplay between the inflammatory cells also requires further study. Using novel compounds with actions at more than one histamine receptor will provide both interesting scientific knowledge and possibly better treatments.

Acknowledgements

We thank the following for support: COST Action BM0806, Grant SAF2011-26518, BIO-267, CIBERER is an initiative of ISCIII (Spain), grant no. LD11010 of the MEYS of the Czech Republic. Thanks are due to Dr. R. Montañez for preparing figure 4.2.

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